STIC-ILL

Fr m: Seharaseyon, Jegatheesan
Sent: Wednesday, December 04, 2002 10:59 AM
To: STIC-ILL
Subject: 09/604,378

Importance: High

Please obtain the following articles. Thanks.

1. ACCESSION NUMBER: 2000159268 MEDLINE
DOCUMENT NUMBER: 20159268 PubMed ID: 10694945
TITLE: Prevention and treatment of chemotherapy- and radiotherapy-induced oral mucositis: a review.
AUTHOR: Plevova P
CORPORATE SOURCE: Department of Radiotherapy, University Hospital of Ostrava, Ostrava-Poruba, Czeck Republic.. pavlina.plevova@fnspo.cz
SOURCE: ORAL ONCOLOGY, (1999 Sep) 35 (5) 453-70. Ref: 225
Journal code: 9709118. ISSN: 1368-8375.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

2. ACCESSION NUMBER: 95211031 MEDLINE
DOCUMENT NUMBER: 95211031 PubMed ID: 7696971
TITLE: IL-11, a pleiotropic cytokine: exciting new effects of IL-11 on gastrointestinal mucosal biology.
AUTHOR: Keith J C Jr; Albert L; Sonis S T; Pfeiffer C J; Schaub R G
CORPORATE SOURCE: Genetics Institute, Inc., Cambridge, Massachusetts.
SOURCE: STEM CELLS, (1994) 12 Suppl 1 79-89; discussion 89-90.
Journal code: 9304532. ISSN: 1066-5099.
PUB. COUNTRY: United States

3. ACCESSION NUMBER: 2000453978 MEDLINE
DOCUMENT NUMBER: 20464824 PubMed ID: 11012229
TITLE: The clinical development of recombinant human interleukin 11 (NEUMEGA rhIL-11 growth factor).
AUTHOR: Kaye J A
CORPORATE SOURCE: Clinical Research/Hematology, Genetics Institute, Inc., Cambridge, Massachusetts 02140, USA.
SOURCE: STEM CELLS, (1996) 14 Suppl 1 256-60. Ref: 26
Journal code: 9304532. ISSN: 1066-5099.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

4. DOCUMENT NUMBER: 97392673 PubMed ID: 9245489
TITLE: Mitigating effects of interleukin 11 on consecutive courses of 5-fluorouracil-induced ulcerative mucositis in hamsters.
AUTHOR: Sonis S T; Van Vugt A G; McDonald J; Dotoli E; Schwertschlag U; Szklut P; Keith J
CORPORATE SOURCE: Division of Oral Medicine Oral and Maxillofacial Surgery, and Dentistry, Brigham & Women's Hospital, Boston, MA 02115, USA.
SOURCE: CYTOKINE, (1997 Aug) 9 (8) 605-12.

Seyon.

J.Seharaseyon
Art Unit 1647
CM1 10D16
10B19 MB
Phone:(703)-305-1112
Fax: (703)-746-5177

MITIGATING EFFECTS OF INTERLEUKIN 11 ON CONSECUTIVE COURSES OF 5-FLUOROURACIL-INDUCED ULCERATIVE MUCOSITIS IN HAMSTERS

S.T. Sonis,[1,2] A.G. Van Vugt,[1] J. McDonald,[1] E. Dotoli,[1] U. Schwertschlag,[3] P. Szklut,[3] J. Keith[3]

Ulcerative mucositis is a painful, debilitating and dose-limiting toxicity of cancer chemotherapy. Current treatment is largely palliative and no adequate preventive treatment exists. Recently, we reported that recombinant human(rh) interleukin II (IL-11) favourably modified the course of mucositis following a single stomatotoxic regimen of 5-flurouracil in hamsters. Although potentially beneficial, the clinically relevant issue of mucositis and myelosuppression during multicourse chemotherapy treatment was not addressed. The present study was undertaken to evaluate the effect of rhIL-11 on two consecutive courses of mucositis and myelosuppression in hamsters. Ulcerative mucositis was induced using a standardized protocol consisting of 5-fluorouracil (60 mg/kg) on days 1 and 2 followed by superficial irritation of the buccal mucosa on day 4. Animals treated with 100 μg of rhIL-11 for 12 consecutive days following each regimen of chemotherapy experienced a reduction in the incidence, severity, and duration of mucositis, a reduction in weight loss, and less morbidity and mortality relative to control animals. Bone marrow cellularity and function was not adversely affected by rhIL-11 treatment. The present study is consistent with the potential use of rhIL-11 in treating patients at risk of developing ulcerative mucositis while undergoing intensive multicourse chemotherapy treatment.

Ulcerative mucositis is a painful, debilitating, and often dose-limiting toxicity of cancer chemotherapy.[1] The oral mucosa, like the rest of the gastrointestinal mucosa, is often adversely affected by the non-specific, direct toxicity of antineoplastics.[2,3] An overall frequency of 40% has been reported to be associated with various agents including 5-fluorouracil,[4] methotrexate,[5,6] cytaribine,[7] and etoposide.[7] Ulcerative mucositis results in destruction of the oral mucosa as an anatomic barrier. The mouth thus becomes a portal of entry for enteric bacterial, viral and fungal organisms. Chemotherapy-induced myelosuppression develops soon after mucositis, causing the mouth to be a frequently identifiable source of sepsis in the granulocytopenic cancer patient.[8,9]

Current therapy for mucositis is largely palliative; no adequate preventive treatment exists. Previous animal studies have shown that cytokine-mediated biological manipulation of the oral mucosa can modify the course of mucositis. Epidermal growth factor, which stimulates epithelial proliferation exacerbates the condition.[10] In contrast, both transforming growth factor beta3[11] and interleukin 11,[12] favourably modify the course of ulcerative mucositis.

Interleukin 11 (IL-11) is a 178-amino acid polypeptide with a molecular weight of 19 kDa.[13] Various studies have shown IL-11 to be a multifunctional cytokine expressed in a broad range of tissues.[14] The activities with the most biotherapeutic relevance to cancer chemotherapy include stimulation of bone marrow, platelet, and neutrophil recovery[15,16] as well as small intestinal mucosal cell recovery following cytoblative treatment.[17]

Recently, we reported that recombinant human (rh) IL-11 favourably modified the course of mucositis produced by a single dose of 5-fluorouracil in hamsters.[12] Treatment with rhIL-11 reduced the incidence, severity, and duration of mucositis, weight loss, and mortality in addition to stimulating platelet production in a dose-dependent manner. Although beneficial effects were observed, the clinically relevant issue of mucositis and myelosuppression

From the [1]Division of Oral Medicine, Oral and Maxillofacial Surgery, and Dentistry, Brigham & Women's Hospital, Boston, MA, [2]Department of Oral Medicine and Diagnostic Sciences, Harvard School of Dental Medicine, Boston, MA, [3]Genetics Institute, Cambridge, MA

Correspondence to: Stephen T. Sonis, Brigham & Women's Hospital, Department of Dentistry, Carrie M. Hall, 3rd Floor, Boston, MA 02115

Received 14 October 1996; revised and accepted for publication 27 March 1997

1043–4666/97/080605 + 8 $25.00/0/ck970208

KEY WORDS: animal model/antineoplastics/hamster/interleukin 11/mucositis

CYTOKINE, Vol. 9, No. 8 (August, 1997: 605–612)

during multicourse chemotherapy treatment was not addressed. The present study was thus undertaken with three objectives: to evaluate the effect of rhIL-11 on two consecutive courses of chemotherapy-induced ulcerative mucositis; to establish the optimal regimen of rhIL-11; and, to determine if rhIL-11 exacerbates the myelosuppressive effects associated with two consecutive courses of 5-fluorouracil.

RESULTS

During cycle 1, treatment with rhIL-11 markedly reduced the severity and duration of mucositis (Fig. 1). Control X had significantly more severe mucositis than both Regimen A and B on days 6 through 14 and 7 through 14, respectively (t-test, $P < 0.05$). During cycle 2, only Regimen A was beneficial, especially during the development of mucositis.

The incidence of animals with moderate to severe mucositis, defined as a score equal to or greater than 4, was evaluated. During cycle 1, Control X had a significantly higher incidence of animals with moderate to severe mucositis (Fig. 2) than both Regimens A and B, on days 8 through 12 and 7 through 14, respectively (chi square, $P < 0.05$). During cycle 2, only Regimen A had a favorable effect.

Serum samples tested positive, as shown by ELISA, for the presence of anti-rhIL-11 antibody on days 14, 21, and 35. The mean titre was 2.2 ± 0.3. The incidence, severity and duration of mucositis in Regimen A was similar during both cycles despite the presence of anti-rhIL-11 antibody. Regimen B, however, was effective during cycle 1 but ineffective during cycle 2.

Regimen A minimized weight loss (Fig. 3) relative to control groups during both cycles. Significant differences were observed on days 4 through 14 (t-test, $P < 0.05$). In contrast, animals given Regimen B experienced a significant reduction in weight loss on days 5 through 12 of cycle 1 but had greater weight loss than control animals during cycle 2.

Bone marrow cellularity was within normal limits for all groups on days 14 and 35 (Table 1). However, Control X had significantly greater bone marrow cellularity than Regimens A and B on day 14 (Mann–Whitney U test, $P < 0.05$). Regimen A was also significantly greater than Regimen B on day 14. On day 35, both Control X and Regimen A exhibited comparable cellularity that was greater than that of Control Y and Regimen B. However, no significant differences were noted.

Analysis of peripheral blood samples showed that animals in Regimen A had higher platelet and white blood cell counts on days 14 and 35 relative to all other groups (Tables 2 and 3). Animals in Regimen A had significantly higher mean white blood cell counts than Regimen B on day 14 (Mann–Whitney U test, $P < 0.05$). Mean platelet and white blood cell counts of animals in Regimen A were significantly

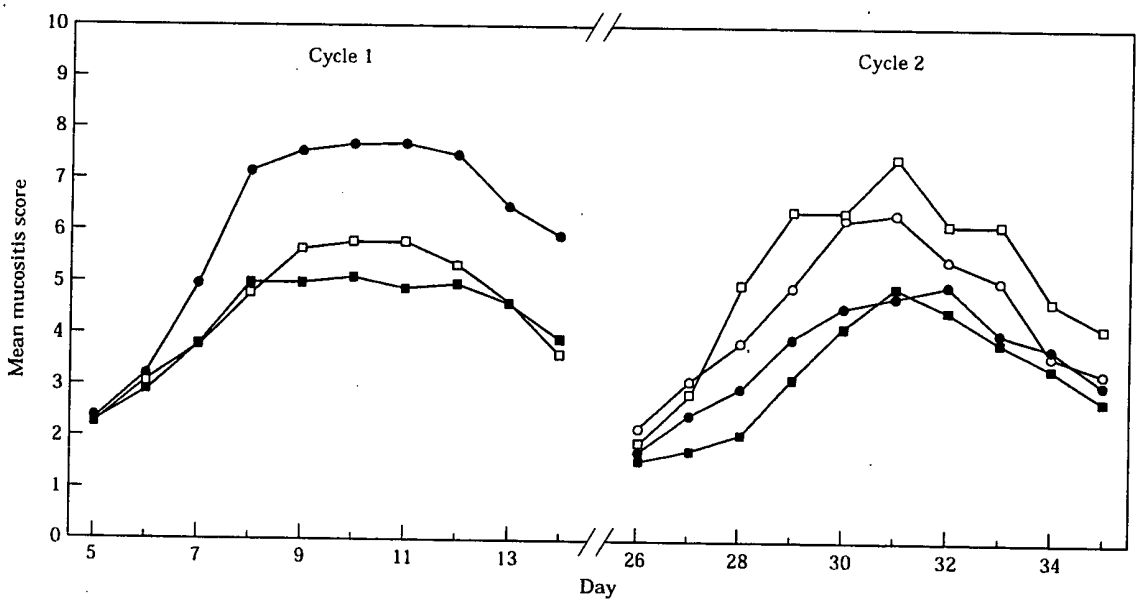

Figure 1. Mean musocitis scores for all groups by day.

During cycle 1, animals treated with 100 μg rhIL-11 for 12 consecutive days following chemotherapy (Regimen A) or 50 μg of rhIL-11, twice daily, one day before and one day following chemotherapy (Regimen B) had significantly less severe mucositis on days 6–14 and 7–14, respectively (t-test, $P < 0.05$). During cycle 2, only Regimen A was beneficial, especially during the development of mucositis. (●), vehicle control X ($n = 70$); (○), vehicle control Y ($n = 12$); (■), rhIL-11 Regimen A ($n = 24$); (□), rhIL-11 Regimen B ($n = 24$).

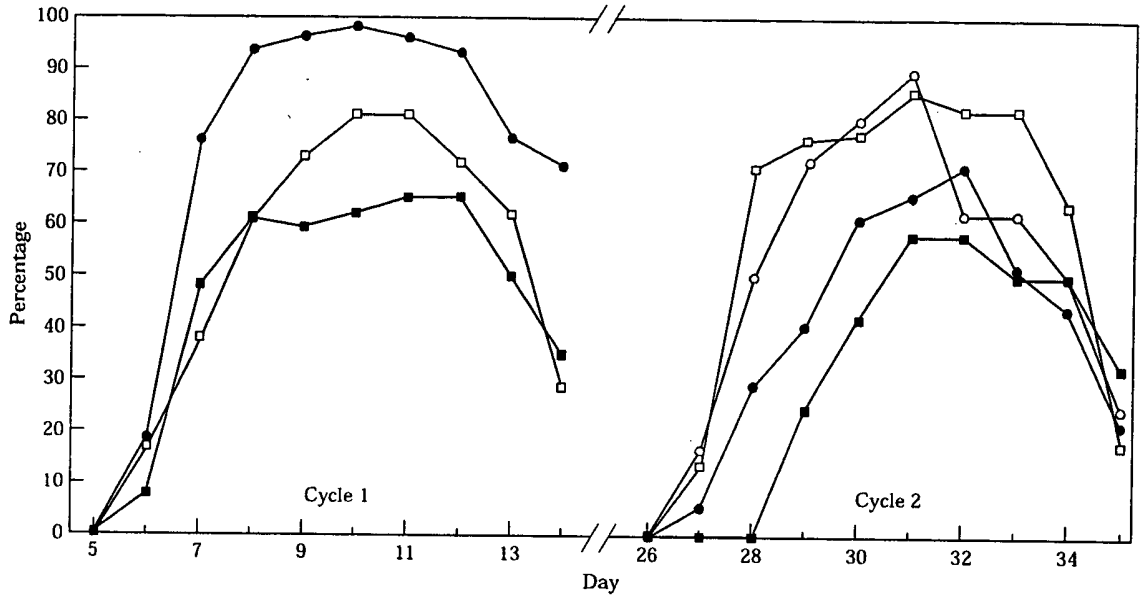

Figure 2. Incidence of moderate to severe mucositis for all groups by day.

The incidence of moderate to severe mucositis, defined as a score greater than or equal to 4, within each group was evaluated during both cycles. During cycle 1, the control group had a significantly higher incidence of animals with moderate to severe mucositis than groups treated with rhIL-11 Regimen A on days 8 through 12 and Regimen B on days 7 through 14 (chi square, $P < 0.05$). During cycle 2 only Regimen A was effective. For explanation of symbols, see Figure 1.

higher than all other groups on day 35. Animals in Regimen B had higher platelet counts than other groups on day 21.

Treatment with rhIL-11 reduced mortality (Fig. 4) as a greater proportion of animals in Regimen A and B survived during both cycles 1 and 2 than control

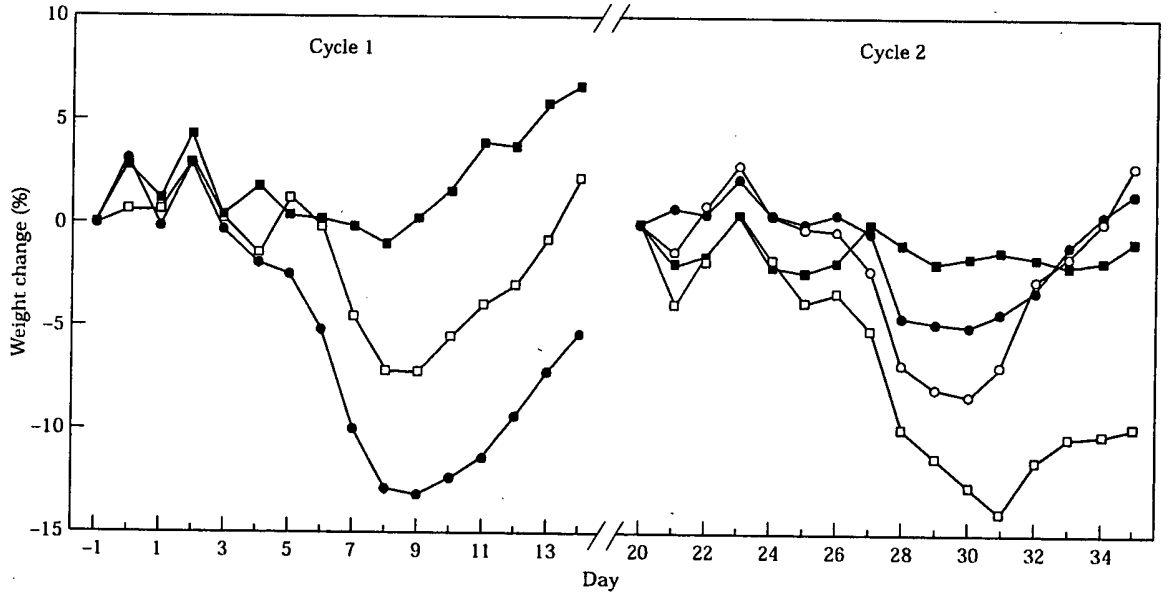

Figure 3. Relative weight change (%) for all groups by day.

Animals treated with 100 μg rhIL-11 for twelve consecutive days following chemotherapy (Regimen A) experienced less weight loss than untreated animals throughout the study. Significant differences were observed on days 4 through 14 (t-test, $P < 0.05$). Animals given 50 μg of rhIL-11, twice daily, one day before and one day following chemotherapy (Regimen B), experienced significantly less weight loss relative to control animals on days 5 through 12 (t-test, $P < 0.05$) but more weight loss during the second cycle. For explanation of symbols, see Figure 1.

TABLE 1. Average bone marrow cellularity ± 1 SD ($n = 3$ per group) on days 14 and 35.

Group	Day 14	Day 35
Control X	93 ± 3	90 ± 9
Control Y		79 ± 11
Regimen A	83 ± 3	90 ± 5
Regimen B	73 ± 3	78 ± 10

Bone marrow cellularity was within normal limits for all groups on both days. However, Control X had significantly greater cellularity then Regimens A and B on day 14 (Mann–Whitney U, $P < 0.05$). Regimen A was also significantly greater than Regimen B on day 14. On day 35, both Control X and Regimen A had comparable cellularity that was greater than that of Control Y and Regimen B, but not statistically significant.

groups. At the conclusion of cycle 1, 64% of animals in Control X remained, whereas 83 and 88% remained in Regimen A and B, respectively. At the end of cycle 2, 64% of animals in Control X and 67% in Control Y survived, in contrast to 86% in Regimen A and 79% in Regimen B. Figure 5 shows the trends in cumulative survival for each group over the course of the study. Again, treatment with rhIL-11 was beneficial in animals given two consecutive courses of chemotherapy. Sixty-seven per cent of animals treated with Regimen A and 61% of animals treated with Regimen B survived, whereas only 42% survived in Control X.

DISCUSSION

Ulcerative mucositis continues to be an important dose-limiting complication of cancer chemotherapy. Although the use of colony-stimulating factors and broad spectrum antibiotics to treat chemotherapy-induced myelosuppression has become commonplace, an adequate preventive treatment for mucosal toxicity has not yet been developed.[18,19]

Mucosal toxicity is initially the consequence of the cytotoxic and cytostatic effects of antineoplastics

TABLE 2. Mean platelet count (K/μl) ± 1 SD ($n = 3$ per group) on days 14, 21 and 35.

Group	Day 14	Day 21	Day 35
Control X	2014 ± 697	816 ± 169	991 ± 314
Control Y			903 ± 462
Regimen A	2571 ± 1579	699 ± 161	2717 ± 1169
Regimen B	1149 ± 494	1010 ± 268	874 ± 208

Animals given 100 μg of rhIL-11 for twelve consecutive days following chemotherapy (Regimen A) had higher platelet counts on day 14 and significantly higher counts on day 35 (Mann–Whitney, $P < 0.05$) relative to all other groups. Animals given 50 μg of rhIL-11, twice daily, one day before and one day following chemotherapy (Regimen B) had higher platelet counts relative to other groups on day 21.

TABLE 3. Mean white blood cell count (K/μl) ± 1 SD ($n = 3$ per group) on days 14, 21 and 35.

Group	Day 14	Day 21	Day 35
Control X	10.5 ± 0.7	10.6 ± 5.9	7.6 ± 2.4
Control Y			4.9 ± 2.1
Regimen A	17.6 ± 5.4	5.7 ± 1.8	20.1 ± 6.5
Regimen B	10.3 ± 2.5	6.7 ± 3.9	6.7 ± 3.6

Animals given 100 μg of rhIL-11 for 12 consecutive days following chemotherapy (Regimen A) had significantly higher white blood cell counts than Regimen B on day 14 and all groups on day 35 (Mann–Whitney, $P < 0.05$).

on the stem cells within the basal layer of the oral epithelium (direct stomatotoxicity).[20] Subsequent secondary local infection may follow as myelosuppression becomes maximal causing both exacerbation of the local condition and predisposition of the host to sepsis (indirect stomatotoxicity). Given the rate of epithelial renewal, direct stomatotoxicity generally begins within 5 days of the administration of drug. In contrast, indirect stomatotoxicity corresponds to the development of myelosuppression and is usually not a factor until 10 days following treatment.[21]

Previous animal studies have shown a strong relationship between cytokine-mediated biological manipulation of the oral mucosa and an alteration in the course of mucositis. For example, treatment with epidermal growth factor (EGF), which increases the rate of epithelial proliferation, severely exacerbates the condition.[10] In contrast, treatment with transforming growth factor beta (TGF-β), which inhibits epithelial proliferation, reduces the severity of the condition when given before chemotherapy.[11]

rhIL-11 is potentially advantageous in that it has been shown to have myelopoietic activity and to reduce gastrointestinal mucosal toxicity following cytoablative treatment.[15,16,17] Previous studies have shown rhIL-11 to reduce the severity, incidence, and duration of oral mucositis in hamsters given a single stomatotoxic course of 5-fluorouracil.[12] In addition to favourably modifying mucositis, animals treated with IL-11 experienced less weight loss as well as less morbidity and mortality. The observed effects were dose dependent. Although IL-11 did demonstrate myelopoietic activity in hamsters, the effect of IL-11 on the course of mucositis was mediated at the level of the mucosa, as a reduction in the severity of mucositis was observed prior to any increase in peripheral blood counts.

In the present study, the clinically relevant issue of mucositis and myelosuppression during multicourse chemotherapy treatment was addressed. Animals treated with 100 μg of IL-11 for twelve consecutive days following chemotherapy (Regimen A) experienced a reduction in the incidence, severity, and duration of mucositis, weight loss, and mortality during both

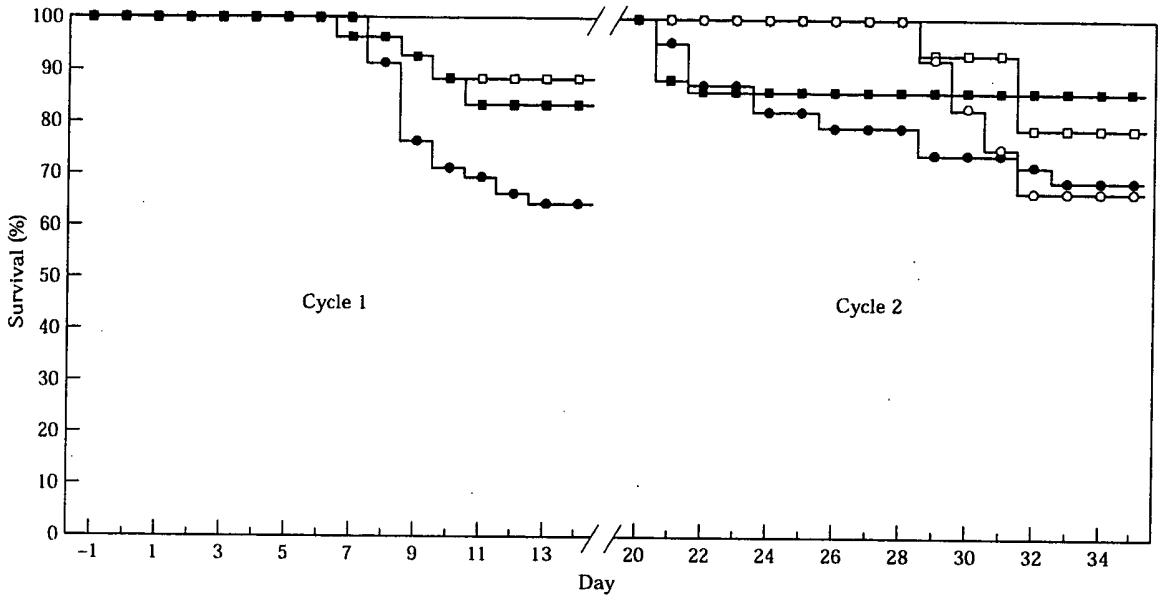

Figure 4. Survival (%) subsequent to each course of 5-fluorouracil for all groups by day.

Animals killed for histological and peripheral blood studies were censored from this comparison. At the conclusion of cycle 1, 64% of animals in Control X remained, whereas 83 and 88% remained in Regimen A and B, respectively. At the end of cycle 2, 64% of animals in Control X and 67% in Control Y survived, in contrast to 86% in Regimen A and 79% in Regimen B. However, no significant differences were noted.

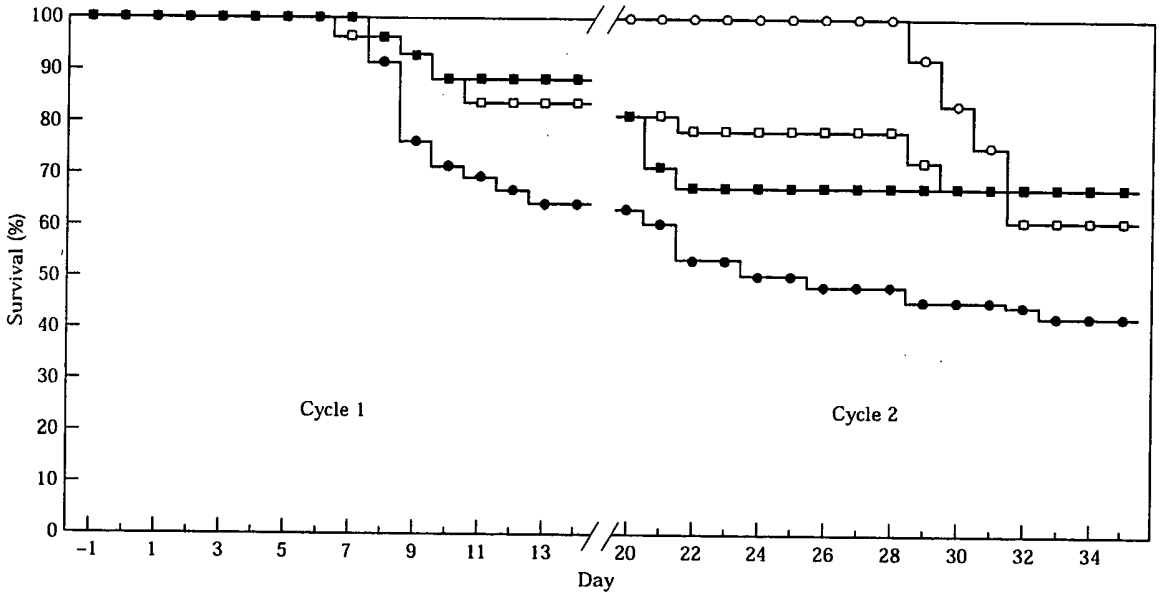

Figure 5. Cumulative survival (%) for all groups by day.

Animals killed for histological and peripheral blood studies were censored from this comparison. Treatment with rhIL-11 was beneficial in animals given two consecutive courses of chemotherapy. Sixty-seven per cent of animals treated with Regimen A and 61% of animals treated with Regimen B survived, whereas only 42% survived in the Control X. However, no significant differences were noted.

CYTOKINE, Vol. 9, No. 8 (August, 1997: 605–612)

cycles. It could, however, be argued that Regimen A was somewhat less effective relative to Control X following the second course of 5-fluorouracil. This diminished efficacy may be due to natural selection. The majority of animals in the control group most vulnerable to the cytotoxicity of 5-fluorouracil perished during cycle 1 resulting in a sample population of hamsters more fit to tolerate 5-fluorouracil during cycle 2. The findings that Control X demonstrated less severe mucositis than Control Y during cycle 2 seems to support this hypothesis.

The presence of anti-rhIL-11 antibody may also have influenced the course of mucositis during cycle 2. Regimen A may have been somewhat efficacious during cycle 2 because rhIL-11 was present in sufficient quantity and for a long enough period to saturate the neutralizing antibody and still bind its receptor. In contrast, Regimen B may have been ineffective during cycle 2 because rhIL-11 was sufficiently neutralized by anti-rhIL-11 antibody.

Myelosuppression was not exacerbated by IL-11 treatment as marrow cellularity was within normal limits. Although IL-11 has a definite impact on direct stomatotoxicity through its action on the mucosa, its myelopoietic activity may contribute to minimizing indirect stomatotoxicity through stimulation of the marrow as peripheral blood counts were higher than untreated animals on days 14 and 35. Further studies need to be conducted in order to elucidate the relationship between direct and indirect stomatotoxicity. The present study is, however, consistent with previous investigations which demonstrated the potential use of rhIL-11 in treating patients at risk of developing ulcerative mucositis and may prove to be beneficial to patients undergoing intensive multicourse chemotherapy treatment.

MATERIALS AND METHODS

The effect of rhIL-11 on the course of chemotherapy-induced ulcerative mucositis following two stomatotoxic courses of 5-fluorouracil was evaluated. Recombinant human (rh) IL-11 (Genetics Institute, Cambridge, MA) purified from *Escherichia coli* was used. All procedures were conducted in accordance with guidelines set by the Harvard Medical Area Standing Committee on Animals.

Animals

Male LVG Golden Syrian hamsters (Charles River Laboratories, Wilmington, MA), aged 5–6 weeks, were used. Animals were caged in small groups and fed standard hamster chow and water *ad libitum*.

Mucositis induction and evaluation

To evaluate the effect of rhIL-11 on two consecutive courses of mucositis, a well-established animal model was used. All procedures were done under anaesthesia with diethyl ether. To induce a single course of mucositis, 5-fluorouracil was administered (60 mg/kg) by intraperitoneal injection on days 0 and 2. The left cheek pouch mucosa was irritated on day 4. Animals were weighed and observed

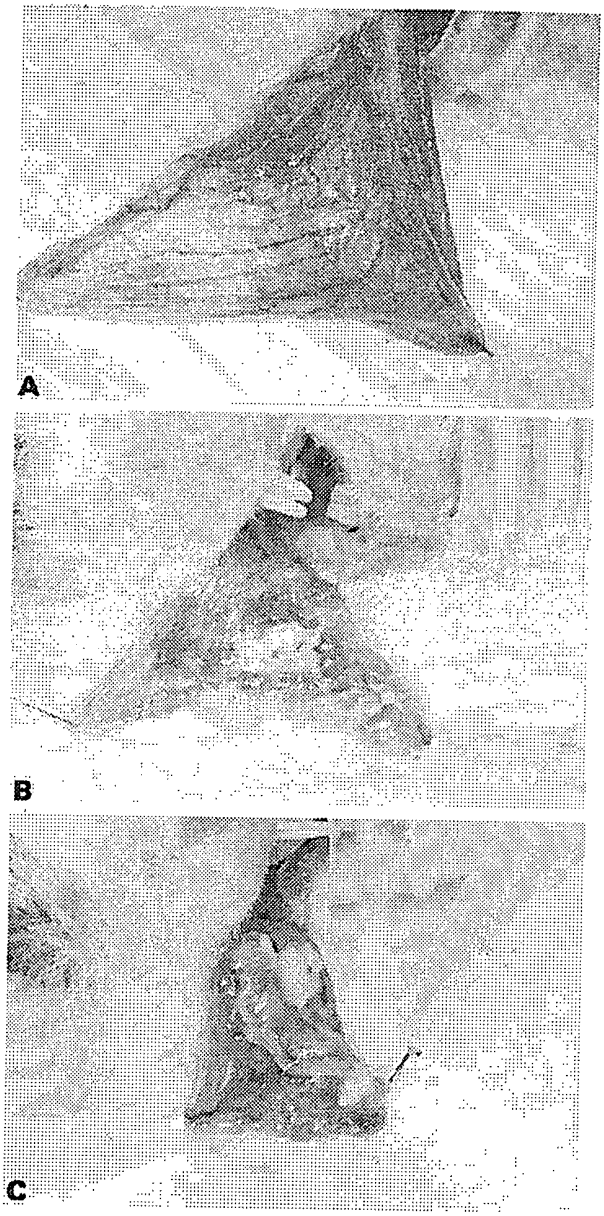

Figure 6. Representative photographs of mild, moderate and severe mucositis.

A 10-point scale was used by three independent observers to grade the severity of mucositis. Mild mucositis (A) was defined as mucosal erythema with vasodilation of the buccal cheek pouch and equalled a score of 1 to 3 on the 10-point scale. Moderate mucositis (B) equalled a score of 4 to 6 and was defined as ulceration (<0.5 cm) with pseudomembranous formation, erythema and vasodilation. Severe mucositis (C) was given a score greater than 6 and was defined as diffuse ulceration (≥ 0.5 cm) with large areas of necrosis, pseudomembrane, erythema and vasodilation.

TABLE 4. The four groups of hamsters used in the study.

Group	*n*/group	Treatment	Cycle 1	Cycle 2
Control X	70	Vehicle, s.c., q.d.	days 3–14	days 24–35
Control Y	12	Vehicle, s.c., q.d.		days 24–35
Regimen A	24	100 μg rhIL-11, s.c., q.d.	days 3–14	days 24–35
Regimen B	24	50 μg rhIL-11, s.c., b.i.d.	days 1 and 3	days 20 and 24

daily through day 14. Mucositis was evaluated (see below) on days 5 through 14 (cycle 1). This induction protocol consistently produces moderate-to-severe mucositis, 20–25% weight loss, and 30–35% mortality in hamsters. As in humans, ulceration manifests five to seven days following the initiation of chemotherapy and resolves within two to three weeks.[22]

Because the primary objective of this study was to evaluate the effect of IL-11 on two consecutive stomatotoxic courses of 5-fluorouracil, the induction protocol was repeated seven days following resolution of the first course of mucositis (day 21). The seven-day rest period also permitted bone marrow recovery. Animals were given the same dose of 5-fluorouracil on days 21 and 23. The right cheek pouch mucosa was irritated on day 25. Animals were weighed and observed daily. Mucositis was evaluated on days 26 through day 35 (cycle 2).

Outcome measures included severity of mucositis, weight change, bone marrow cellularity, platelet count, white blood cell count, anti-rhIL-11 titre, and survival. To evaluate mucositis, animals were anaesthetized and the cheek pouch was everted, immobilized, and photographed as previously reported.[22] At the conclusion of the study, all film was developed simultaneously. Photographs were numbered, randomized, and graded blindly by three independent observers using a 10-point scale in which mild mucositis equalled a score of 1 to 3 (Fig. 6A); moderate, 4 to 6 (Fig. 6B); and severe, greater than 6 (Fig. 6C).

On days 14 and 35, three animals from each group were randomly selected and killed to obtain bone marrow and peripheral blood samples. The left femur was dissected and fixed in Zenker's solution, post-fixed in 10% phosphate-buffered formalin, decalcified, processed, embedded, and stained with haemotoxylin and eosin. Bone marrow was assessed for cellularity in a blinded fashion by a haematologist. Peripheral blood samples were analysed by Coulter counter. On day 21, three animals from groups 1, 3 and 4 (see below) were randomly selected and sacrificed in order to obtain peripheral blood samples only.

To determine if rhIL-11 induced an immune response in hamsters the serum fractions of peripheral blood samples were tested for the presence of anti-rhIL-11 antibodies in an enzyme-linked immunosorbent assay (ELISA). Samples were incubated with rhIL-11 drug product, which was immobilized on an ELISA plate. After incubation, the plate was washed, and bound antibody was detected and visualized by protein A conjugated to horseradish peroxidase (HRP) and *o*-phenylenediamine (OPD) substrate containing hydrogen peroxide (H_2O_2). As a means to monitor assay performance, negative (normal hamster plasma diluted 1:50) and positive R06A05 (a polyclonal antibody specific for IL-11) controls were included on each plate. Each sample was initially tested, in duplicate, at a single dilution of 1:50 and their reactivity was evaluated relative to a "cutpoint" optical density (OD; 490 nm), which is defined as twice the mean OD of the negative control. Samples generating an OD less than the cutpoint were considered to be negative and not tested further; samples that generated an OD greater than or equal to the cutpoint OD were considered to be positive. To confirm the initial ELISA results and to determine the antibody titre (the log of the dilution that generates an OD greater than the cutpoint), positive samples were re-assayed in a dilution series.

Test groups

One hundred and thirty hamsters were randomly divided into four groups. These test groups were then evaluated, as shown in Table 4.

Vehicle consisted of phosphate-buffered saline (PBS) and 0.5% hamster serum. rhIL-11 (or placebo) was administered by subcutaneous injection. Total injection volume was 0.5 ml. Animals given Regimen A were treated with 100 μg of rhIL-11, once daily, for 12 consecutive days following chemotherapy. Animals given Regimen B were treated with 50 μg of rhIL-11, twice daily, for a cumulative dose of 100 μg, one day before and one day following chemotherapy. Neither group received rhIL-11 and chemotherapy simultaneously. A second control group (Control Y) provided a single exposure mucositis baseline to which animals receiving multiple chemotherapy cycles could be compared during cycle 2.

Statistical significance between groups was determined using Student's *t*-test, Mann–Whitney U test and chi-square analysis with a critical value of 0.05.

REFERENCES

1. Sonis ST, Clark J (1991) Prevention and management of oral mucositis induced by antineoplastic therapy. Oncology 5:11–16.

2. Mitchell EP, Schein PS (1984) Gastrointestinal toxicity of chemotherapeutic agents. In Perry MC, Yarbo JW (eds) Toxicity of Chemotherapy, Clinical Oncology Monographs, Grune and Stratton, Orlando, pp. 269–295.

3. Peterson DE (1992) Oral toxicity of chemotherapeutic agents. Semin Oncol 19:478–491.

4. Caballero GA, Ausman RK, Quebbeman EJ (1985) Long-term, ambulatory continuous iv infusion of 5-FU for the treatment of advanced adenocarcinomas. Cancer Treatment Reports 69:13–15.

5. Balis FM, Savitch JL, Bleyer WA, Reaman GH, Poplack DG (1985) Remission induction of meningeal leukemia with high-dose intravenous methotrexate. J. Clin Oncol 3:385–489.

6. Roth BJ, Sledge GW, Williams SD, Meyer SC, Ansari R, Fisher WB (1991) Methotrexate, vinblastine, doxorubicin, and cisplatin in metastatic breast cancer. Cancer 68:248–252.

7. Bishop JF, Joshua DE, Lowenthal RM, Kronenberg H, Whiteside MG, Cobcroff R, Dodds A, Wolf M, Manoharan A (1986) A phase I-II study of cytosine arabinoside, daunorubicin, and VP16-213 in adult patients with acute non-lymphocytic leukemia. Aust NZ J Med 16:48–51.

8. Bergmann OJ (1989) Oral manifestations and fever in immunocompromised patients with hematological malignancies. Eur J Clin Microbiol Infect Dis 8:207–213.

9. Donnelly JP, Muus P, Horrevorts AM, Sauerwein RW, De Pauw BE (1993) Failure of clindamycin to influence the course of severe oromucositis associated with streptococcal bacteremia in allogeneic bone marrow recipients. Scand J Infect Dis 25:43–50.

10. Sonis ST, Costa JW, Evitts SM, Lindquist LE, Nicolson M (1992) Effect of epidermal growth factor on ulcerative mucositis in hamsters that receive cancer chemotherapy. Oral Surg Oral Med Oral Path 74:749–755.

11. Sonis ST, Lindquist L, Van Vugt A, Stewart AA, Stam K, Qu GY, Iwata KK, Haley JD (1994) Prevention of chemotherapy-induced ulcerative mucositis by transforming growth factor beta-3. Cancer Res 54:1135–1138.

12. Sonis S, Muska A, O'Brien J, Van Vugt A, Langer-Safer P, Keith J (1995) Alteration in the frequency, severity and duration of chemotherapy-induced mucositis in hamsters by interleukin-11. Oral Onc Eur J Canc 31B:261–266.

13. Neben S, Turner K (1993) The biology of interleukin 11. Stem Cells 11:156–162.

14. Du XX, Williams DA (1994) Interleukin-11: a multifunctional growth factor from the hematopoietic microenvironment. Blood 83:2023–2030.

15. Du XX, Neben T, Goldman S, Williams DA (1993) Effects of recombinant human interleukin-11 on hematopoietic reconstitution in transplant mice: acceleration of recovery of peripheral blood neutrophils and platelets. Blood 81:27–34.

16. Leonard JP, Quinto CM, Kozitza MK, Neben TY, Goldman SJ (1994) Recombinant human interleukin-11 stimulates multilineage hematopoietic recovery in mice after a myelosuppressive regimen of sublethal irradiation and carboplatin. Blood 83:1499–1506.

17. Du XX, Doerschuk CM, Orazi A, Williams DA (1994) A bone marrow-stromal derived growth factor, interleukin-11, stimulates recovery of small intestinal mucosal cells after cytoablative therapy. Blood 83:33–37.

18. Brincker H, Christensen BE (1993) Acute mucocutaneous toxicity following high-dose hydroxyurea. Cancer Chemoth Pharmacol 32:48–51.

19. Lokich J, Anderson N, Bern M, Coco F, Zipoli T, Moore C, Gonsalves L (1991) Dual modulation of 5-fluorouracil using leucovorin and hydroxyurea. Cancer 68:744–746.

20. Squier CA (1990) Mucosal alterations. NCI Monographs 9:169–172.

21. Woo SB, Sonis ST, Monopoli MM, Sonis AL (1993) A longitudinal study of oral ulcerative mucositis in bone marrow transplant recipients. Cancer 72:1612–1617.

22. Sonis ST, Tracey C, Shklar G, Jenson J, Florine D (1990) An animal model for mucositis induced by cancer chemotherapy. Oral Surg Oral Med Oral Path 69:437–443.